TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. § 371		Attorney's Docket Number 054160-5060 U.S. Application No. Unassigned 10/049666
International Application. No.	International Filing Date	Priority Date Claimed
PCT/EP00/08011	August 16, 2000	August 16, 1999

Title of Invention: PHARMACEUTICAL AGENT COMPRISING A BENZAMIDE DERIVATIVE AS ACTIVE INGREDIENT

Applicants For EO/EO/US: Tsuneji SUZUKI, Tomoyuki ANDO, Masahiko ISHIBASHI, Masahiro SAKABE and Ikuo SAKAI

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. § 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. § 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. § 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. § 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. § 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. § 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. § 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. § 371(c)(3)).
9. ☒ An oath or declaration of the inventors (35 U.S.C. § 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. § 371(c)(5)).

Items 11. to 14. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. § 3.28 and § 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☒ Other items or information:
    a. PCT/IB/308
    b. PCT/IPEA/409
    c. PCT/ISA/210

U.S. APPLICATION NO.	INTERNATIONAL APPLICATION NO.	ATTORNEY DOCKET NUMBER
10/049666 Unassigned	PCT/EP00/08011	054160-5060

15. ☒ The following fees are submitted:

Basic National Fee (37 C.F.R. § 1.492(a)(1)-(5)):

Search Report has been prepared by the EPO or JPO.....$890.00
International preliminary examination fee paid to USPTO (37 C.F.R. § 1.482).....$710.00
No international preliminary examination fee paid to USPTO (37 C.F.R. § 1.482) but international search fee paid to USPTO (37 C.F.R. § 1.445(a)(2)).....$740.00
Neither international preliminary examination fee (37 C.F.R. § 1.482) nor international search fee (37 C.F.R. § 1.445(a)(2)) paid to USPTO.....$1,040.00
International preliminary examination fee paid to USPTO (37 C.F.R. § 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT = $890.00

Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 C.F.R. § 1.492(e)). $

Claims	Number Filed	Number Extra	Rate	
Total Claims	36 - 20 =	16	X $18.00	$ 288.00
Independent Claims	1 - 3 =	0	X $84.00	$
Multiple dependent claim(s) (if applicable)			+ $280.00	$ 280.00
			TOTAL OF ABOVE CALCULATIONS	$ 1458.00
			Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 C.F.R. §§ 1.9, 1.27, 1.28)	-$
			SUBTOTAL =	**$ 1458.00**
			Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. § 1.492(f)).	+$
			TOTAL NATIONAL FEE =	**$ 1458.00**
			Fee for recording the enclosed assignment (37 C.F.R. § 1.21(h)). The Assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§ 3.28, 3.31). $40.00 per property	$ 40.00
			TOTAL FEES ENCLOSED =	**$ 1498.00**
			Amount to be refunded	$
			Amount to be charged	$ 1498.00

a. ☒ Please charge Deposit Account No. 50-0310 in the amount of **$1498.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

b. ☒ **Except** for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. § 1.16 and § 1.17 which may be required, or credit any overpayment to Deposit Account No. 50-0310.

Customer No. 09629
SEND ALL CORRESPONDENCE TO:
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Telephone: (202) 739-3000
Facsimile: (202) 739-3001

Lynn E. Eccleston
Reg. No. 35,861

Submitted: February 15, 2002

PATENT
ATTORNEY DOCKET NO. 054160-5060

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of : Tsuneji SUZUKI et al.

U.S. Application No.: To Be Assigned — Group Art Unit: To Be Assigned

Date of National Stage Entry : February 15, 2002 — Examiner: To Be Assigned

Based on PCT/EP00/08011
Filed : August 16, 2000

For: PHARMACEUTICAL AGENT COMPRISING A BENZAMIDE DERIVATIVE AS ACTIVE INGREDIENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

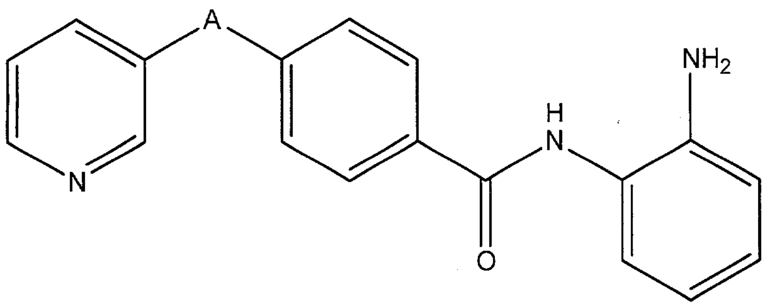
Prior to the examination of the above-identified application on the merits, please amend the application as follows:

In the claims:

Please cancel claims 1-17.

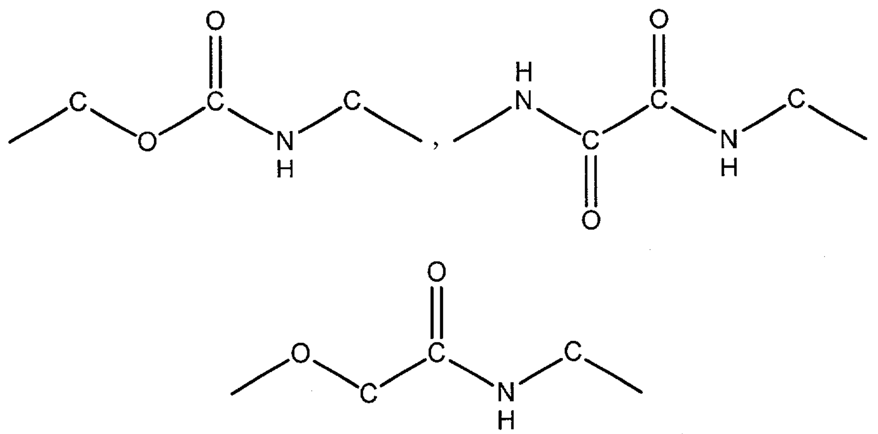
Please add the following claims 18-31:

18. A pharmaceutical composition, comprising: (a) a benzamide derivative represented by formula (1):



(1)

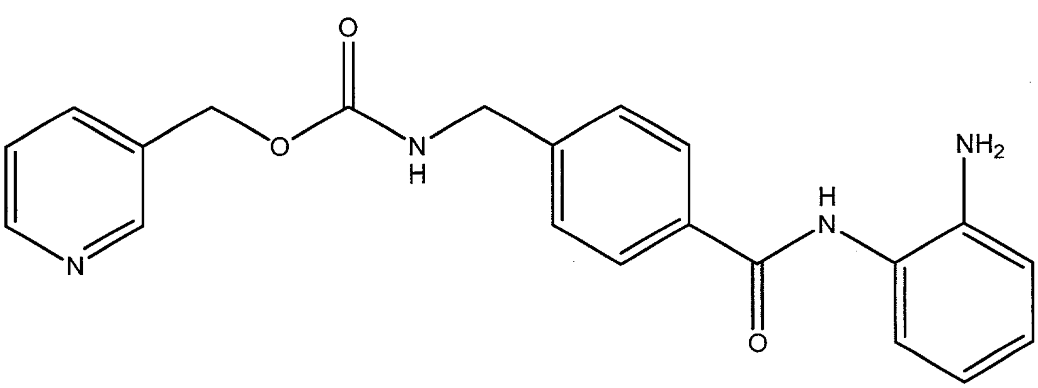
wherein A represents any one of the structures of formula (2):



(2)

or a pharmaceutically acceptable salt thereof, and (b) at least one additive selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent.

19. The pharmaceutical composition according to claim 18, wherein said benzamide derivative is represented by formula (3):



(3)

20. The pharmaceutical composition according to claim 18, wherein said excipient is D-mannitol.

21. The pharmaceutical composition according to claim 18, wherein said disintegrant is at

least one disintegrant selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium.

22. The pharmaceutical composition according to claim 18, wherein said binder is hydroxypropyl cellulose.

23. The pharmaceutical composition according to claim 18, wherein said lubricant is at least one lubricant selected from the group consisting of magnesium stearate and talc.

24. The pharmaceutical composition according to claim 18, wherein said coating agent is hydroxypropyl methylcellulose.

25. The pharmaceutical composition according to claim 18, wherein said solvent is at least one solvent selected from the group consisting of a propylene glycol, dimethylacetamide, and polyethylene glycol.

26. The pharmaceutical composition according to claim 18, further comprising at least one compound selected from the group consisting of an organic acid salt, an amino compound, and an inorganic basic substance.

27. The pharmaceutical composition according to claim 26, wherein said organic acid salt is at least one organic acid salt selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate.

28. The pharmaceutical composition according to claim 26, wherein said amino compound is at least one amino compound selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine, L-glutamate, and carbachol.

29. The pharmaceutical composition according to claim 26, wherein said inorganic basic substance is at least one inorganic basic substance selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

30. The pharmaceutical composition according to any one of claims 18-29, wherein the pharmaceutical composition is a solid composition which comprises granules prepared by a dry granulation method.

31. The pharmaceutical composition according to any one of claims 18-29, wherein the pharmaceutical composition is a liquid composition with an adjusted pH ranging from about 4 to about 12.

REMARKS

Claims 1-17 in the application have been cancelled without waiver, disclaimer or prejudice. New claims 18-31 have been added by this Preliminary Amendment.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTION PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Lynn E. Eccleston
Reg. No. 35,861

Dated: February 15, 2002

MORGAN, LEWIS & BOCKIUS LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
(202) 739-3000

DESCRIPTION

PHARMACEUTICAL AGENT COMPRISING A BENZAMIDE DERIVATIVE AS ACTIVE INGREDIENT

Field of Invention

The present invention relates to a pharmaceutical composition and in particular to a pharmaceutical formulations comprising as an active ingredient a benzamide derivative or a pharmaceutically acceptable salt thereof, that is useful as a pharmaceutical agent, in particular an anticancer agent.

Background Art

Benzamide derivatives or pharmaceutically acceptable salts thereof according to the present invention have an ability of inhibiting histone deacetylating enzymes and of inducing differentiation, and are useful as therapeutic or ameliorating agents for diseases that are involved in cellular growth such as malignant tumors, autoimmune diseases, skin diseases, infections, blood vessel diseases, allergic diseases, gastrointestinal disorders, hormonal diseases, diabetes mellitus, and the like, enhancers of the effect of gene therapy, or immunosuppressants. In particular, they are effective as anti-tumor agents and are effective against hematopoietic organ tumors and solid tumors (Japanese Unexamined Patent Publication (Kokai) No. 10-152462).

However, though the benzamide derivatives and pharmaceutically acceptable salts thereof of the present invention are stable per se, they become unstable and decompose markedly over time when combined with additives such as light silicic acid anhydride, lactose, corn starch, carboxymethyl cellulose, magnesium alminate metasilicate, titanium oxide, polyethylene glycols and polysorbates that are commonly used in order to produce dosage forms suitable for oral, percutaneous, or tissue administration.

Furthermore, when they are formulated into tablets

by the wet granulation, the most common granulation method of preparing solid formulations, they become further unstable and yield, in large quantities, decomposed products different from simple hydrolyzates, resulting in pharmaceutical formulations in which the ratio of an active ingredient is as low as about 0.001 to 25%, which noticeably decompose, and therefore which are unsuitable as pharmaceutical solid formulations to be provided as medical drugs. Also, pharmaceutical formulations that employ ingredients commonly used for liquids such as polysorbates, polyethylene glycols, and glycerin were unstable. Thus it was difficult to use, as medical drugs, pharmaceutical formulations that contain a benzamide derivative or a pharmaceutically acceptable salt thereof at about 0.001 to 25% as an active ingredient.

Disclosure of Invention

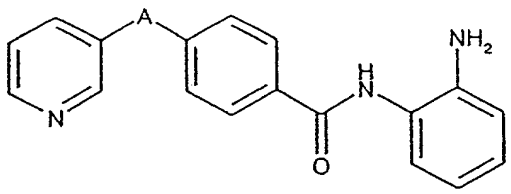
The present invention is intended to enhance the stability of compositions containing as an active ingredient a pharmaceutically useful benzamide derivative or a pharmaceutically acceptable salt and to effectively use them as a pharmaceutical formulation.

In order to solve the above problems, intensive research was conducted on the effects of temperature, humidity, and physicochemical properties on the solutions, powders, and solid shaped products to which a benzamide derivative or a pharmaceutically acceptable salt thereof has been added. As a result, the inventors have found that the problem of instability of an active ingredient can be solved and stable and excellent pharmaceutical formulations can be produced by using selectively, among the additives commonly used for pharmaceutical formulations, those additives that do not easily induce decomposition of benzamide derivatives, adding an organic acid salt, an amino compound and an inorganic basic substance, and the like as a stabilizer, producing using the dry granulation or adjusting pH in

the range of 4 to 12, preferably in the range of pH 7 to 11, and thereby have completed the present invention.

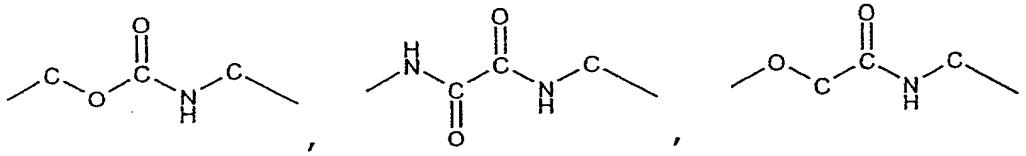
Thus, the present invention relates to

[1] a pharmaceutical formulation comprising a benzamide derivative represented by the formula (1):



(1)

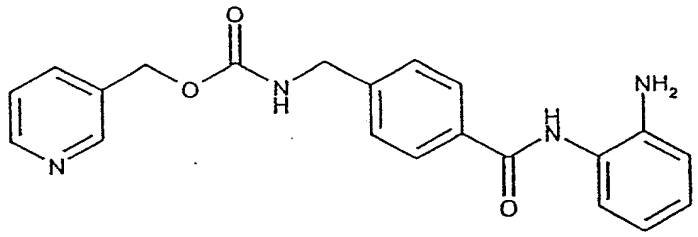
wherein A represents a structure shown by any one of the formula (2):



(2)

or a pharmaceutically acceptable salt thereof, and one or more than one additive selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent;

[2] as a preferred embodiment the pharmaceutical formulation of the above [1] wherein said benzamide derivative is represented by the formula (3);



(3)

[3] as a preferred embodiment the pharmaceutical formulation of the above [1] or [2] wherein said

excipient is D-mannitol;

[4] as another preferred embodiment the pharmaceutical formulation of any one of the above [1] to [3] wherein said disintegrant is one or more than one selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium;

[5] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [4] wherein said binder is hydroxypropyl cellulose;

[6] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [5] wherein said lubricant is one or more than one selected from magnesium stearate and talc;

[7] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [6] wherein said coating agent is hydroxypropyl methylcellulose;

[8] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [7] wherein said solvent is one or more than one selected from the group consisting of propylene glycol, dimethylacetamide, and polyethylene glycol;

[9] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [8] wherein said formulation further comprises one or more than one selected from the group consisting of an organic acid salt, an amino compound, and an inorganic basic substance;

[10] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [9] wherein said organic acid salt is one or more than one selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate;

[11] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [9] wherein said amino compound is one or more than one selected from

the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol;

[12] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [9] wherein said inorganic basic substance is one or more than one selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia;

[13] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [12] wherein the formulation is a solid formulation which comprises preparing granules by a dry granulation method; and

[14] as a preferred embodiment, the pharmaceutical formulation of any one of the above [1] to [13] wherein the formulation is a liquid formulation and pH is adjusted within the range of 4 to 12.

Embodiment for Carrying Out the Invention

The present invention will now be explained in further detail below.

The pharmaceutical formulations as used herein generally mean those that have been produced by formulating one or more additives with an active ingredient or active ingredients and that have been formulated into shapes suitable for use in various dosage forms of medical drugs.

According to the present invention, solid formulations, in particular powders, can be produced by adding to the active ingredient one or more than one additives that do not easily induce decomposition by using a method conventionally used by a person skilled in the art. Examples of additives that do not easily induce decomposition include: D-mannitol as an excipient; partly

pregelatinized starch, carboxymethylstarch sodium, and carmellose calcium as a disintegrant; hydroxypropyl cellulose as a binder; magnesium stearate and talc as a lubricant; and hydroxypropyl methyl cellulose as a coating agent. One or more than one of them can be used.

According to the present invention, solid formulations, in particular granules, tablets, and capsules can be produced by a dry granulation method in which additives that do not easily induce decomposition are added to the active ingredient, mixed in a shaker such as a granulator and a V-type mixer, compression-molded by a roller compactor after the mixture in a shaker, and further crushed by a power mill thereby to form granules.

Furthermore, more stable granules, tablets, and capsules can be obtained by adding to the active ingredient one or more than one selected from the group consisting of an organic acid salt such as monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate; an amino compound such as tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; an inorganic basic substance such as sodium carbonate, potassium carbonate, lithium carbonate, strontium carbonate; ammonium carbonate, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, strontium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia, and by granulating in the dry granulation method.

When an organic acid salt, an amino compound or an inorganic basic substance is added, additives such as excipients, disintegrants, binders, lubricants, and coating agents can be used without limitation. Examples include, lactose, lactose anhydride, D-mannitol, corn

starch, and crystalline cellulose as an excipient; hydroxypropyl cellulose, polyvinylpyrrolidone, methyl cellulose, glycerin, and water as a binder; carmellose, calcium carmellose, low-substitution hydroxypropyl cellulose, and partly pregelatinized starch as a disintegrant; magnesium stearate, calcium stearate, stearic acid, and talc as a lubricant; and hydroxypropyl methyl cellulose, methacrylic acid copolymer, and hydroxypropyl methyl cellulose phthalate as a coating agent.

In accordance with the present invention, stable liquids, syrups, injections, emulsions, suspensions, suppositories, soft capsules whose contents are liquid, or hard capsules whose contents are liquid and the like can be produced by dissolving an active ingredient into solvents that do not easily induce the decomposition of the active ingredient such as propylene glycol and dimethylacetamide, by using a method conventionally used by a person skilled in the art.

More stable liquids, syrups, injections, emulsions, suspensions, suppositories, soft capsules whose contents are liquid, or hard capsules whose contents are liquid and the like can be produced by dissolving in a solvent one or more than one ingredients, selected from the group consisting of an organic acid salt such as monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate and trisodium citrate; an amine compound such as tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; an inorganic basic substance such as ammonium carbonate, disodium phosphate, sodium carbonate, potassium carbonate, lithium carbonate, strontium carbonate, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, strontium bicarbonate, sodium hydroxide and ammonia, and by adjusting pH in the

range of 4 to 12 with an acid or a base.

As used herein, acids or bases mean organic bases, inorganic bases, organic acids, or inorganic acids that can be used as medical drugs. Organic bases mean tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, arginine, and the like. Inorganic bases mean sodium hydroxide, ammonium water, potassium bicarbonate, potassium carbonate, sodium bicarbonate, sodium carbonate, and the like. Organic acids mean citric acid, succinic acid, acetic acid, tartaric acid, lactic acid, and the like. Inorganic acids mean hydrochloric acid, sulfuric acid, phosphoric acid and the like.

In order to produce lyophilized formulations, according to the present invention, an active ingredient is mixed with a conventionally known solvent such as one or more than one solvent selected from the group consisting of purified water, macrogol, propylene glycol, polysorbate and dimethylacetamide; to a resulting composition are further added one or more than one additive selected from the group consisting of sugars; gelatin; dextrin; an organic acid salt such as monosodium fumarate, sodium alginate, sodium glutamate, sodium dehydroacetate, sodium erythorbate, trisodium citrate, and arginine-glutamate; an amine compound such as tris(hydroxymethyl)aminomethane, ammonia water, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, glycine, and carbachol; an inorganic basic substance such as ammonium carbonate, disodium phosphate, sodium carbonate, sodium bicarbonate and potassium bicarbonate; and then pH of the resulting composition is adjusted to 4 to 12, as desired, with an acid or a base, and the composition is freeze-dried under a reduced pressure.

The pharmaceutical formulations of the present

invention can be administered by any method depending on various dosage forms, the age and sex of the patient, the severity of disease, and other conditions. For example, tablets, pills, liquids, syrups, suspensions, emulsions, granules, and capsules may be orally administered, injections may be intravenously administered either singly or in an admixture with a conventional supplement such as glucose and an amino acid, and, as needed, may be administered singly intramuscularly, subcutaneously, or intraperitoneally. Lyophilized formulations reconstituted with solvent such as saline and purified water may be administered intravenously singly or in an admixture with a conventional supplement such as glucose, an amino acid and the like, and, as needed, may be administered singly intramuscularly, subcutaneously, or intraperitoneally. Suppositories may be directly administered intrarectally.

Dosages of the pharmaceutical formulations of the present invention are selected as appropriate depending on the method of administration, the age and sex of the patient, the severity of disease, and the like. Generally the daily dosage of an active ingredient compound is preferably in the range of about 0.0001 to 100 mg/kg, and for pharmaceutical formulations in the unit dosage form an active ingredient compound is preferably included at a range of about 0.001 to 1,000 mg.

Benzamide derivatives, active ingredients of the present invention, or pharmaceutically acceptable salts thereof can be produced by a method described in, for example, Japanese Unexamined Patent Publication (Kokai) No. 10-152462.

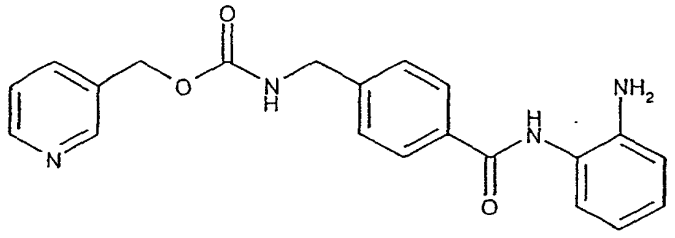
Medical drugs as used herein mean, in addition to anticancer agents, agents for the treatment and/or amelioration of autoimmune diseases, skin diseases, infections, diseases of blood vessels, allergic diseases, gastrointestinal disorders, hormonal diseases, diabetes

mellitus, and the like, enhancers of the effect of gene therapy, or immunosuppressants.

Examples

The present invention will now be explained in more detail with reference to the following compound, N-(2-aminophenyl)-4-[N-(pyridine-3-yl)methoxycarbonyl]aminomethyl benzamide (compound 1), in Examples and Reference Examples. It is to be noted, however, that the present invention is not limited by these examples in any way.

Compound 1



Example 1.

Compound 1 (1 g) was mixed with 1 g each of D-mannitol, partly pregelatinized starch, carmellose calcium, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, magnesium stearate, and talc to prepare a powder formulation. Similarly, lactose, corn starch, crystalline cellulose, carmellose, light-weight silicic acid anhydride, magnesium aluminum metasilicate, and titanium oxide were mixed to prepare a comparative control sample. After these formulations were stored at an air-tight condition at 60°C for 4 weeks and at an open condition at 40°C and at a relative humidity of 75% for 3 months, they were subjected to HPLC analysis. The percentage (%) of degradation products relative to the active ingredient was shown in Table 1. The powder formulation prepared by mixing 1:1 with D-mannitol, partially gelatinized starch, carmellose calcium, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, magnesium stearate or talc was stable.

Table (1): Stability of various powders

Additive	Storage condition: 60°C air-tight 4 weeks	Storage condition: 40°C 75% RH open 3 months
Comparative control sample		
None	0.18	0.19
Lactose	0.55	0.44
Corn starch	0.39	0.34
Crystalline cellulose	0.25	0.61
Carmellose	0.43	0.41
Light-weight silicic acid anhydride	5.87	10.01
Magnesium aluminum metasilicate	17.94	5.45
Titanium oxide	1.75	0.82
Example		
D-mannitol	0.21	0.21
Partially gelatinized starch	0.21	0.34
Carmellose calcium	0.30	0.21
Hydroxypropyl cellulose	0.20	0.20
Magnesium stearate	0.22	0.20
Hydroxypropyl methyl cellulose	0.27	0.21
Talc	0.36	0.23

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 2.

Pharmaceutical formulations a, b, c, d, e, and f shown in Table (2) were prepared in the following procedure. Thus, compound 1 and D-mannitol divided into 1/8, 2/8, and 5/8 of the prescribed amount were serially added under mixing using a granulator to prepare homogeneous powders. Furthermore, 1/2 of the prescribed amount of magnesium stearate was added thereto and was mixed in a V-shaped mixer for 20 minutes, compression-molded by a roller compactor, and further crushed by a power mill to prepare granules. Subsequently, carboxymethyl starch sodium of the prescribed amount and 1/2 of the prescribed amount of magnesium stearate were added and mixed in a V-shaped mixer, made into tablets by tabletting machine to obtain samples a, b, c, d, e, and f.

Table (2): Formulation for tablets (unit: mg)

Ingredient/number	Sample of the present invention					
	a	b	c	d	e	f
Active ingredient	5.0	1.0	1.0	1.0	1.0	1.0
D-mannitol	56.0	60.0	60.0	60.0	60.0	60.0
Carboxymethyl starchsodium	3.3	3.3	3.3	3.3	3.3	3.3
Magnesium stearate	0.7	0.7	0.7	0.7	0.7	0.7
Tris(hydroxymethyl) aminomethane	-	-	0.5	-	-	-
Potassium bicarbonate	-	-	-	0.5	-	-
Sodium carbonate	-	-	-	-	0.5	-
Potassium carbonate	-	-	-	-	-	0.5
Total	65.0	65.0	65.5	65.5	65.5	65.5

Reference Example 1.

D-mannitol, partially gelatinized starch, carmellose calcium, magnesium stearate, hydroxypropyl cellulose, polyvinylpyrrolidone K30, or the like which is comparatively stable when mixed with Compound 1 was granulated according to the formulation shown in Table (3) by the wet granulation method and made into tablets by tabletting machine to obtain samples g to i.

Table (3): Formulation for tablets (unit: mg)

Ingredient/number	Sample		
	g	h	i
Active ingredient	1.0	1.0	1.0
D-mannitol	40.6	40.6	40.6
Partially gelatinized starch	17.4	17.4	17.4
Hydroxypropyl cellulose	2.0	2.0	-
Polyvinylpyrrolidone	-	-	2.0
Carmellose calcium	3.3	-	3.3
Magnesium stearate	0.7	0.7	0.7
Total	65.0	65.0	65.0

The percentage (%) of degradation products of compound 1 is shown in Table 4, when samples obtained in Example 2 and Reference Example 1 were stored at an air-tight condition at 60°C for 4 weeks and at an air-tight condition at 80°C for 3 days, and then were subjected to HPLC analysis. The pharmaceutical formulations containing 1 mg of an active ingredient obtained by the wet granulation method shown in Reference Example 1 were unstable as they produced degradation products other than the hydrolyzates, while the samples of the present

invention shown in Example 2, both 5.0 mg- and 1.0 mg-containing formulations, were stable as the production of degradation products remained low.

Table (4): Stability of tablets containing compound 1

Sample		Content (mg)	Storage condition 60°C air-tight 4 weeks (%)	80°C air-tight 3 days (%)
The invention sample	a	5.0	0.4	0.4
	b	1.0	1.0	1.3
	c	1.0	0.7	0.5
	d	1.0	-	0.4
	e	1.0	-	0.4
	f	1.0	-	0.4
Reference example	g	1.0	4.1	3.0
	h	1.0	4.5	2.1
	i	1.0	5.8	5.3

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 3.

Compound 1 was dissolved to a concentration of 20 mg/ml in propylene glycol or dimethylacetamide to prepare liquid formulations. As comparative control samples, compound 1 was dissolved to a concentration of 20 mg/ml in polysorbate 80 or polyethylene glycol 400. Table (5) shows the percentage (%) of degradation products of compound 1 when these formulations were stored at an air-tight condition at 80°C for 3 days. They exhibited good stability when dissolved in propylene glycol or dimethylacetamide.

Table (5): Stability when dissolved in various solvents

Additive	Amount of degradation products (%)
Polysorbate 80	18.1
Polyethylene glycol 400	41.4
Dimethylacetamide	4.1
Propylene glycol	3.6

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 4.

Compound 1 was dissolved to a concentration of 20 mg/ml in polyethylene glycol 400 to prepare a liquid formulation, which was set as a comparative control sample. To the comparative control sample was added each additive at a concentration of 0.05 M to prepare the liquid formulation of the present invention. Table (6) shows the percentage (%) of degradation products of the active ingredients when these formulations and the comparative control samples were stored at an air-tight condition at 80°C for 3 days. Stability was enhanced in the samples to which an organic acid salt, an amino compound, or an inorganic basic substance of the present invention was added.

Table (6): Stability of liquid formulations in which each additive was blended at 0.05 M to compound 1 at 20 mg/ml polyethylene glycol 400
(Storage condition: 80°C, air tight, Storage period: 3 days)

	Additive	Amount of degradation products (%)	pH
Comparative control sample	None	41.4	5.3
The invention sample	Sodium fumarate	21.6	7.0
	Sodium alginate	23.7	6.7
	Sodium dehydroacetate	13.0	8.6
	Sodium erhysorbate	13.2	7.3
	Trisodium citrate	28.2	8.0
	Tris(hydroxymethyl)aminomethane	2.9	10.1
	Monoethanolamine	4.3	11.5
	Diethanolamine	3.9	11.7
	Triethanolamine	9.6	9.4
	Diisopropanolamine	4.7	9.9
	Triisopropanolamine	16.5	8.3
	Dihydroxyaluminum aminoacetate	7.3	6.4
	L-arginine	10.6	11.5
	Creatinine	18.6	7.0
	Sodium glutamate	23.1	-
	Glycine	26.7	-
	L-arginine L-glutamate	29.4	6.5
	Carbachol	32.3	5.4
	Ammonium carbonate	3.6	10.7
	Disodium phosphate	10.8	7.6
	Sodium carbonate	16.8	10.1
	Sodium bicarbonate	25.0	6.5
	Potassium bicarbonate	15.5	7.0
	Ammonia	4.6	11.7

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 5.

To compound 1 dissolved at a concentration of 20 mg/ml in polyethylene glycol 400 was added an equal volume of 0.1 M tris(hydroxymethyl)aminomethane buffer of which pH is varied with hydrochloric acid or sodium hydroxide to prepare a liquid formulation of compound 1 at 10 mg/ml. Table 7 shows the percentage of the degradation products of the active ingredient when these formulations were stored at an air-tight condition at

80°C for 3 days. Samples of the present invention of which pH was adjusted in the range of 7 to 11 exhibited good stability.

Table (7): Stability of 10 mg/ml polyethylene glycol 400 solution of compound 1 when pH was varied (storage condition: 80°C, air-tight, storage period: 3 days)

pH	Amount of degradation products (%)
3.8	98.6
13.2	48.8
7.3	11.9
7.7	8.2
8.5	5.8
9.5	5.6
10.1	4.4

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 6.

Compound 1 was dissolved at a concentration of 20 mg/ml in polyethylene glycol 400, and sodium hydroxide was added thereto so that the final various concentrations can be from 0 mM to 10 mM to prepare liquid formulations. Table 8 shows the percentage of the degradation products of the active ingredient when these formulations were stored at each pH of these formulations and at an air-tight condition at 80°C for 1 day or 7 days. Samples of the present invention of which pH was adjusted in the range of about 7 to 11 exhibited good stability.

Table (8): Relationship between pH and stability of liquid formulations in which compound 1 was dissolved at 20 mg/ml in polyethylene glycol 400, and then sodium hydroxide was added thereto (storage condition: 80°C, air-tight, storage period: 1 day or 7 days)

Concentration of sodium hydroxide (mM)	pH	Amount of degradation products (%)	
		80°C - 1 day	80°C - 7 days
0	5.3	16.0	63.7
0.01	5.9	14.1	60.6
0.1	6.1	14.3	56.0
1.0	7.3	9.7	33.7
2.0	8.9	4.6	12.4
3.0	9.4	5.0	9.8
4.0	10.4	6.0	9.7
5.0	10.8	9.7	11.4
10.0	13.1	71.5	90.6

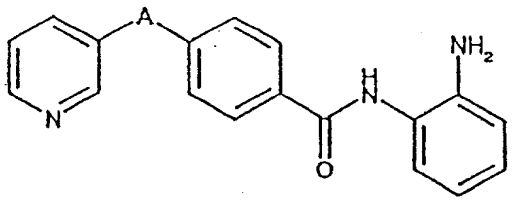
Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Industrial Applicability

Pharmaceutical formulations that produce little degradation products and that are stable enough to be used as medical drugs can be obtained by mixing a pharmaceutically useful benzamide derivatives or a pharmaceutically acceptable salt thereof with additives that do not easily produce degradation products, blending an organic acid salt, an amine compound, or an inorganic basic substance, producing solid formulations by the dry granulation method, and further adjusting the pH of the liquid formulations to 4 to 12.

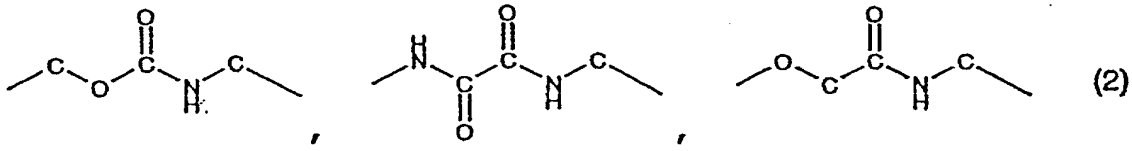
AMENDED CLAIMS

1. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



(1)

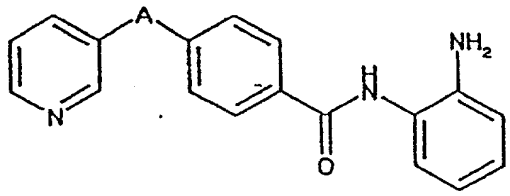
wherein A represents a structure shown by any one of the formula (2):



(2)

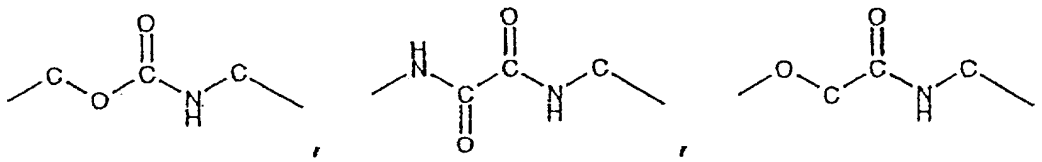
or a pharmaceutically acceptable salt thereof, (ii) one or more than one selected from the group consisting of an organic acid salt, an amino compound and an inorganic basic substance, and (iii) one or more than one selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent.

2. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



(1)

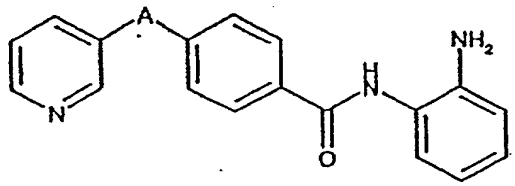
wherein A represents a structure shown by any one of the formula (2):



(2)

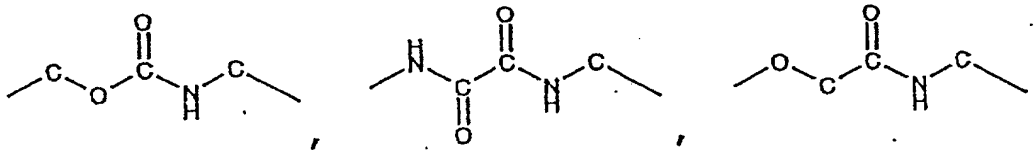
or a pharmaceutically acceptable salt thereof, and (ii) one or more than one selected from the group consisting of D-mannitol, partially gelatinized starch, carboxymethylstarch sodium, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose and dimethylacetamide.

3. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



(1)

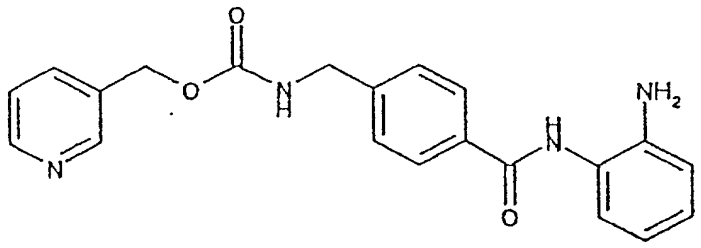
wherein A represents a structure shown by any one of the formula (2):



(2)

or a pharmaceutically acceptable salt thereof, wherein said benzamide derivative or pharmaceutically acceptable salt thereof is dissolved in propylene glycol.

4. The pharmaceutical formulation according to any one of claims 1 to 3 wherein said benzamide derivative is represented by the formula (3):



(3)

5. The pharmaceutical formulation according to claims 1, 2 and 4 wherein said pharmaceutical formulation is a solid formulation.

6. The pharmaceutical formulation according to claims 1 to 4 wherein said pharmaceutical formulation is a liquid formulation.

7. The pharmaceutical formulation according to claims 1, 4 and 5 wherein said excipient is D-mannitol.

8. The pharmaceutical formulation according to any one of claims 1, 4, 5 and 7 wherein said disintegrant is one or more than one selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium.

9. The pharmaceutical formulation according to any one of claims 1, 4, 5, 7 and 8 wherein said binder is hydroxypropyl cellulose.

10. The pharmaceutical formulation according to claims 1, 4, 5 and 7 to 9 wherein said lubricant is one or more than one selected from magnesium stearate and talc.

11. The pharmaceutical formulation according to claims 1, 4, 5 and 7 to 10 wherein said coating agent is hydroxypropyl methylcellulose.

12. The pharmaceutical formulation according to claims 1, 4 and 6 wherein said solvent is one or more than one selected from the group consisting of propylene glycol, dimethylacetamide, and polyethylene glycol.

13. The pharmaceutical formulation according to claims 1 and 4 to 12 wherein said organic acid salt is

one or more than one selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate.

14. The pharmaceutical formulation according to claims 1 and 4 to 13 wherein said amino compound is one or more than one selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate and carbachol.

15. The pharmaceutical formulation according to claims 1 and 4 to 14 wherein said inorganic basic substance is one or more than one selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

16. The pharmaceutical formulation according to claims 1, 2, 4, 5, 7 to 11 and 13 to 15 wherein the formulation is a solid formulation which comprises granules prepared by a dry granulation method.

17. The pharmaceutical formulation according to claims 1 to 4, 6 and 12 to 15 wherein the formulation is a liquid formulation and pH is adjusted within the range of 4 to 12.

ABSTRACT

Stable pharmaceutical formulations can be obtained by mixing a pharmaceutically useful benzamide derivative or a pharmaceutically acceptable salt thereof with additives that do not easily produce degradation products, blending an organic acid salt, an amine compound, and an inorganic basic substance, producing solid formulations by the dry granulation method, and further adjusting the pH of the liquid formulations to 4 to 12. Pharmaceutical formulations that produce little degradation products and that are stable enough to be used as medical drugs can be obtained.

PTO/SB/106 (5-00)
Approved for use through 10/31/02. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Declaration and Power of Attorney for Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

私は、以下に記名された発明者として、ここに下記の通り宣言する：

As a below named inventor, I hereby declare that:

私の住所、郵便の宛先そして国籍は、私の氏名の後に記載された通りである。

My residence, post office address and citizenship are as stated next to my name.

下記の名称の発明について、特許請求範囲に記載され、且つ特許が求められている発明主題に関して、私は、最初、最先且つ唯一の発明者である（唯一の氏名が記載されている場合）か、或いは最初、最先且つ共同発明者である（複数の氏名が記載されている場合）と信じている。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PHARMACEUTICAL AGENT COMPRISING A BENZAMIDE DERIVATIVE AS ACTIVE INGREDIENT

上記発明の明細書はここに添付されているが、下記の欄がチェックされている場合は、この限りでない：

the specification of which is attached hereto unless the following box is checked:

☐ _____ の日に出願され、
この出願の米国出願番号またはＰＣＴ国際出願番号は、
_____ であり、且つ
_____ の日に補正された出願（該当する場合）

☒ was filed on August 16, 2000
as United States Application Number or
PCT International Application Number
PCT/EP00/08011 and was amended on
_____ (if applicable).

私は、上記の補正書によって補正された、特許請求範囲を含む上記明細書を検討し、且つ内容を理解していることをここに表明する。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

私は、連邦規則法典第３７編規則１．５６に定義されている、特許性について重要な情報を開示する義務があることを認める。

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

PTO/SB/106 (5-00)
Approved for use through 10/31/02. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Japanese Language Declaration
（日本語宣言書）

私は、ここに、以下に記載した外国での特許出願または発明者証の出願、或いは米国以外の少なくとも一国を指定している米国法典第３５編第３６５条(a)によるＰＣＴ国際出願について、同第１１９条(a)-(d)項又は第３６５条(b)項に基づいて優先権を主張するとともに、優先権を主張する本出願の出願日よりも前の出願日を有する外国での特許出願または発明者証の出願、或いはＰＣＴ国際出願については、いかなる出願も、下記の枠内をチェックすることにより示した。

I hereby claim foreign priority under Title 35, United States Code, Section 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International application which designated at least one country other than the United States listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filling date before that of the application for which priority is claimed.

Prior Foreign Application(s)
外国での先行出願

Priority Not Claimed
優先権主張なし

(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願日／月／年)	
11-229551 (Pat. Appln.)	Japan	16/August/1999	☐
			☐

私は、ここに、下記のいかなる米国仮特許出願についても、その米国法典第３５編１１９条(e)項の利益を主張する。

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Application No.) (出願番号)	(Filling Date) (出願日)

私は、ここに、下記のいかなる米国出願についても、その米国法典第３５編第１２０条に基づく利益を主張し、又米国を指定するいかなるＰＣＴ国際出願についても、その同第３６５条(c)に基づく利益を主張する。また、本出願の各特許請求の範囲の主題が、米国法典第３５編第１１２条第１段に規定された態様で、先行する米国出願又はＰＣＴ国際出願に開示されていない場合においては、その先行出願の出願日と本国内出願日またはＰＣＴ国際出願日との間の期間中に入手された情報で、連邦規則法典第３７編規則１．５６に定義された特許性に関わる重要な情報について開示義務があることを承認する。

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filling date of the prior application and the national or PCT International filing date of application.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可、係属中、放棄)

私は、ここに表明された私自身の知識に係わる陳述が真実であり、且つ情報と信ずることに基づく陳述が、真実であると信じられることを宣言し、さらに、故意に虚偽の陳述などを行った場合は、米国法典第１８編第１００１条に基づき、罰金または拘禁、若しくはその両方により処罰され、またそのような故意による虚偽の陳述は、本出願またはそれに対して発行されるいかなる特許も、その有効性に問題が生ずることを理解した上で陳述が行われたことを、ここに宣言する。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

PTO/SB/106 (5-00)
Approved for use through 10/31/02. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Japanese Language Declaration
(日本語宣言書)

委任状： 私は本出願を審査する手続を行い、且つ米国特許商標庁との全ての業務を遂行するために、記名された発明者として、下記の弁護士及び／または弁理士を任命する。（氏名及び登録番号を記載すること）

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith (list name and registration number).

書類送付先

Send Correspondence to:

Morgan, Lewis & Bockius LLP
1800 M Street, N.W.
Washington, D.C. 20036-5869

Customer Number: 009629

直通電話連絡先：（氏名及び電話番号）

Direct Telephone Calls to: (name and telephone number)

Robert J. Gaybrick
202-467-7000

唯一または第一発明者氏名	1-A Full name of sole or first inventor: Tsuneji Suzuki
発明者の署名 日付	Inventor's signature: TSUNEJI SUZUKI Date: February 6, 2002
住所	Residence: Mobara-shi, Chiba Japan JP
国籍	Citizenship: Japanese
郵便の宛先 ~~TSUNEJI SUZUKI~~	Post Office Address: c/o Mitsui Chemicals, Inc., 1144, Togo, Mobara-shi, Chiba 297-0017, Japan T.S.
第二共同発明者がいる場合、その氏名	2-A Full name of second joint inventor, if any: Tomoyuki Ando
第二共同発明者の署名 日付	Second inventor's signature: TOMOYUKI ANDO Date: February 6, 2002
住所	Residence: Mobara-shi, Chiba Japan JP
国籍	Citizenship: Japanese
郵便の宛先	Post Office Address: c/o Mitsui Chemicals, Inc., 1144, Togo, Mobara-shi, Chiba 297-0017, Japan

（第三以下の共同発明者についても同様に記載し、署名をすること）

(Supply similar information and signature for third and subsequent joint inventors.)

第三共同発明者	3-D Full name of third joint inventor, if any Masahiko Ishibashi
第三共同発明者　日付	Third inventor's signature　Date Masahiko Ishibashi　February 6, 2002
住　所	Residence Mobara-shi, Chiba Japan
国　籍	Citizenship Japanese
私書箱	Post Office Address c/o Mitsui Pharmaceuticals, Inc., 1900-1,
	Togo, Mobara-shi, Chiba 297-0017, Japan
第四共同発明者	4-D Full name of fourth joint inventor, if any Masahiro Sakabe
第四共同発明者　日付	Fourth inventor's signature　Date Masahiro Sakabe　February 6, 2002
住　所	Residence Mobara-shi, Chiba Japan
国　籍	Citizenship Japanese
私書箱	Post Office Address c/o Mitsui Pharmaceuticals, Inc., 1900-1,
	Togo, Mobara-shi, Chiba 297-0017, Japan

第五共同発明者	5-D Full name of fifth joint inventor, if any Ikuo Sakai
第五共同発明者　日付	Fifth inventor's signature　Date Ikuo Sakai　February 6, 2002
住　所	Residence Mobara-shi, Chiba Japan
国　籍	Citizenship Japanese
私書箱	Post Office Address c/o Mitsui Pharmaceuticals, Inc., 1900-1,
	Togo, Mobara-shi, Chiba 297-0017, Japan
第六共同発明者	Full name of sixth joint inventor, if any
第六共同発明者　日付	Sixth inventor's signature　Date
住　所	Residence
国　籍	Citizenship
私書箱	Post Office Address

（第七以降の共同発明者についても同様に記載し、署名をすること）

(Supply similar information and signature for seventh and subsequent joint inventors.)